Comparability of Alternative Procedures

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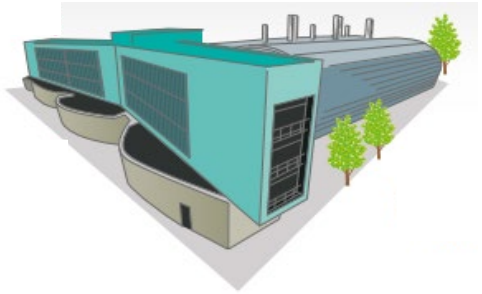
Who's talking ?

Mr Bruno SPIELDENNER



Great team of 10 scientific programme managers and 4 administrative support assistants

French
Strasbourg

Studied Phys-Chem
MSc in Analytical Chemistry
Strasbourg/Marseille

7 years in Pharmaceutical industry in Switzerland
Specialised in Mass spectrometry

Joined CoE/EDQM in 2013
European Pharmacopoeia Department

Since 2022:
Head of Division
Chemistry and Herbals

Work on transversal projects:
General methods chapters, implementation ICH Q3D

Council of Europe

- ★ Established in **1949**
- ★ **46 member states**
- ★ Based in **Strasbourg**
- ★ Founded on three main values: **human rights, democracy and the rule of law**

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Council of Europe ≠ European Council

Parliamentary Assembly
Assemblée parlementaire

Parliamentary Assembly of the Council of Europe ≠ European Parliament

European Parliament

EUROPEAN COURT OF HUMAN RIGHTS
COUR EUROPÉENNE DES DROITS DE L'HOMME

European Court of Human ≠ Court of Justice of the EU

CVRIA

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Committee of Ministers

Parliamentary Assembly

Congress of Local and Regional authorities

European Court of Human Rights

Commissioner of Human Rights

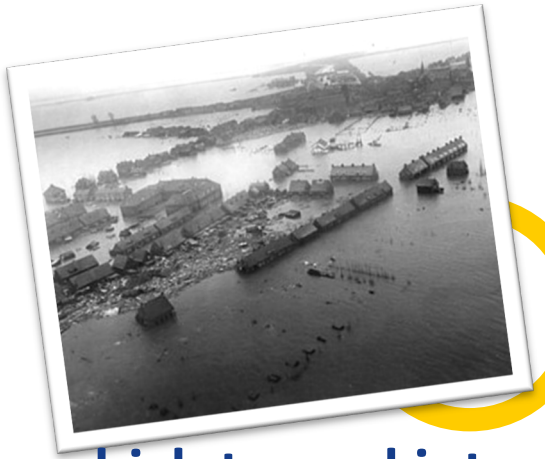
Conference of INGOs

Council of Europe's role in public health

Statute of the Council of Europe 1949

A vision…

- ★ Achieving greater unity between member states and "facilitating their economic and social progress".
- ★ Discussion of questions of common concern, agreements and common action "in economic, social, cultural, scientific, legal and administrative matters".



Humanitarian disaster
North Sea flood of 1953

… which turned into action

- ★ In 1954, the Committee of Ministers set up the European Health Committee to encourage closer cooperation on the promotion of health.
- ★ Create conditions to safeguard and improve health of European citizens.
- ★ was founded in 1964
- ★ Between 2006 and 2009, its public health activities were transferred to the EDQM.

Introduction to EDQM

The EDQM in brief

- Founded in **1964** as the **European Pharmacopoeia** by **a small number of visionary member states**

Today

- Partial Agreement (39 Members & the EU + 33 observers)
- Wide scope of activities- between 2006 and 2009, CoE transferred a number of public health activities to the EDQM.
- The EDQM contributes to **public health and access to good quality medicines and healthcare in Europe**

Key figures

10 Administrative entities

More than **430 staff members** **30 nationalities** and dozens of different professions

3 Sites

Strasbourg x 2

Metz

4 Areas of work

- ★Medicinal products
- ★Substances of Human Origin
- ★Pharmaceutical care
- ★Consumer health

Working with a global network of almost **2 000 experts** from a wide variety of scientific disciplines

- ★**5** steering committees directly answerable to the Committee of Ministers
- ★**1** treaty-based body (EPC)
- ★**2** steering committees (BSP, CEP)
- ★**2** networks
- ★More than **100** expert groups

Contributing all along the pathway to access

Research & Development

European Pharmacopoeia

Marketing & Authorisation

Certification

Production

European Pharmacopoeia

Quality control & release

European Pharmacopoeia
SoHO, FCM and Cosmetics Guides
OMCL, OCCL

Distribution

Healthcare professionals

Pharmaceutical care
Recommendations
Resolutions

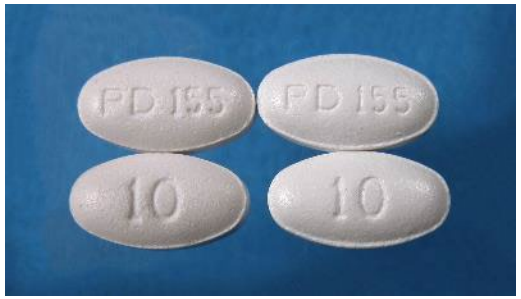
Patients

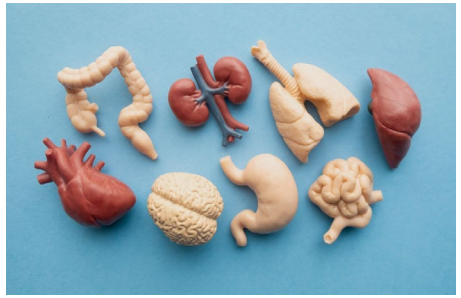
Our added-value for you…
…and your family



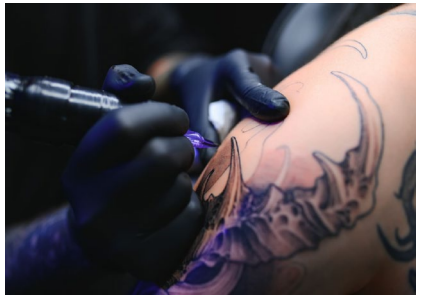










The European Pharmacopoeia

European Pharmacopoeia

Binding in the **39** signatory states of the Ph. Eur. Convention and used as a reference worldwide; **33** observers from all continents

► More than **2 800 documentary standards** for the quality control of medicines

- Cover the whole manufacturing process (*e.g. excipients, medicinal products*)
- All stages of the **life cycle** of a medicine from development through to production and market surveillance
- Analytical procedures verified & standardised

► **About 3000 reference standards shipped to 132 countries**

European Pharmacopeia Commission - treaty-based body - and its expert groups

Biological Standardisation Steering Committee

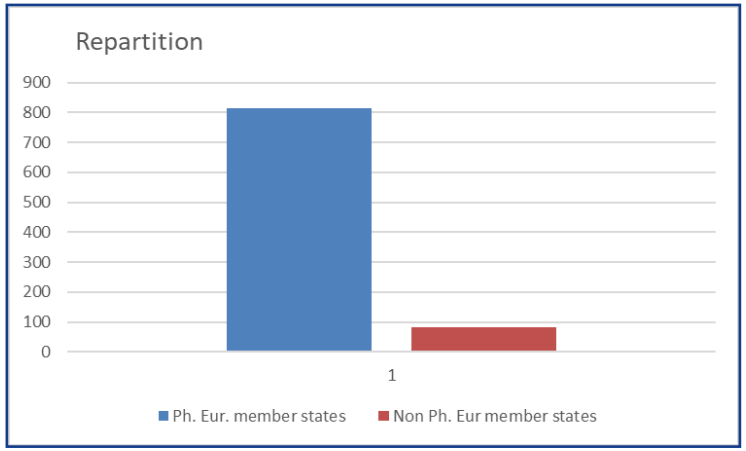
Laboratory, production, storage and distribution

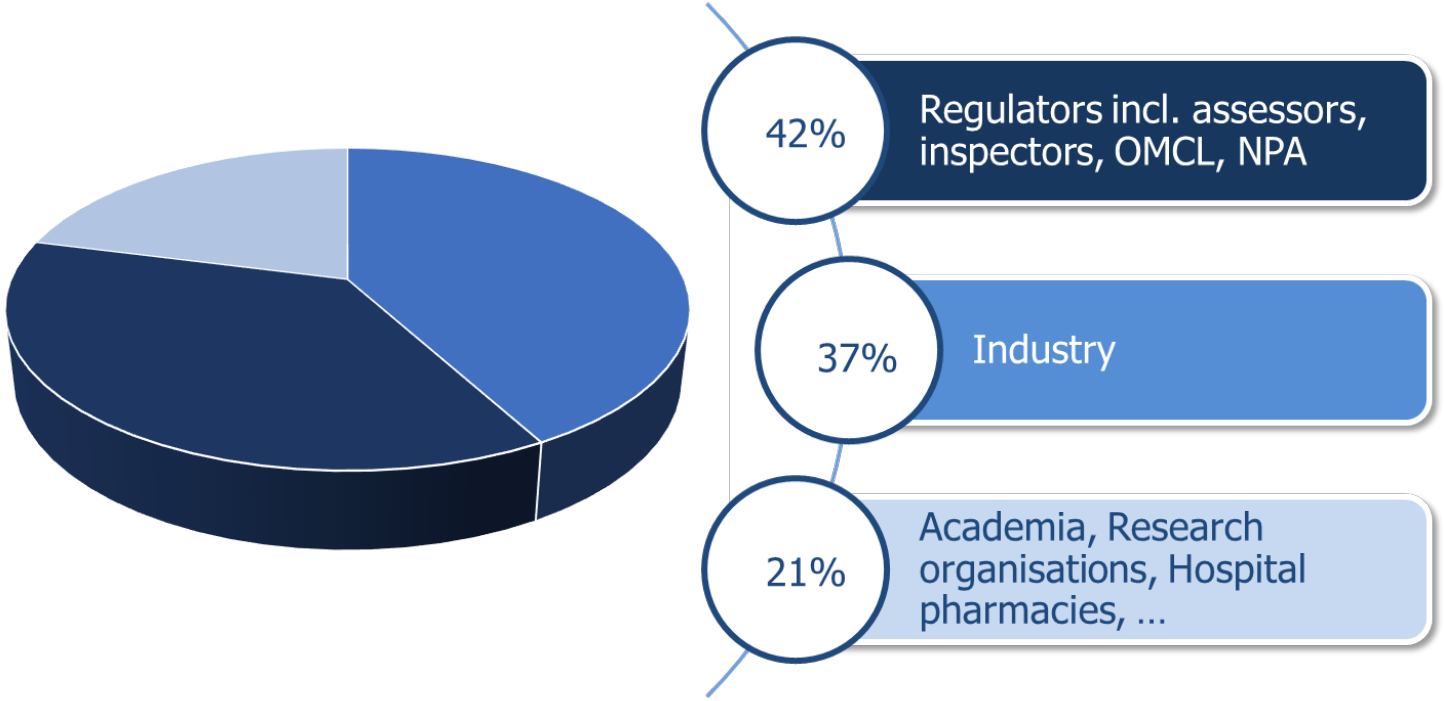
PUBLIC HEALTH IMPACT

- **Ensure equivalent quality and safety of medicinal products throughout Europe and facilitate their free movement in Europe and beyond**

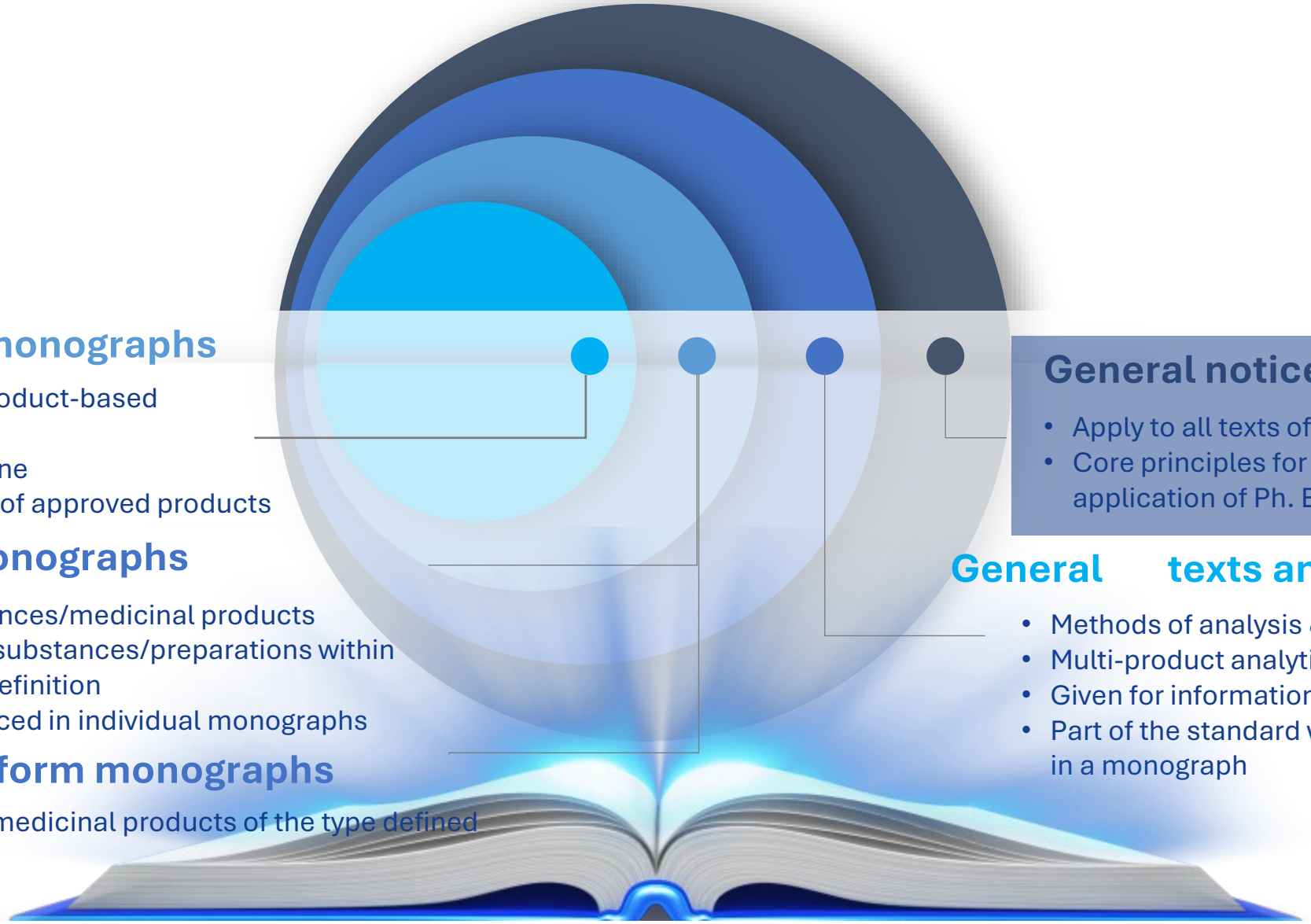
… relying on nearly 900 experts[1] working together …

[1] This number does not include:
- Chairs of Groups
- ad hoc specialists (around 100/year)
- Members of the Ph. Eur. Commission





Ph. Eur.: Content and Structure



Individual monographs

- Substance/product-based
- Specific
- Not stand-alone
- Take account of approved products

General monographs

- Classes of substances/medicinal products
- Mandatory for all substances/preparations within the scope of the definition
- Not cross-referenced in individual monographs

Dosage form monographs

- Apply to all medicinal products of the type defined

General notices

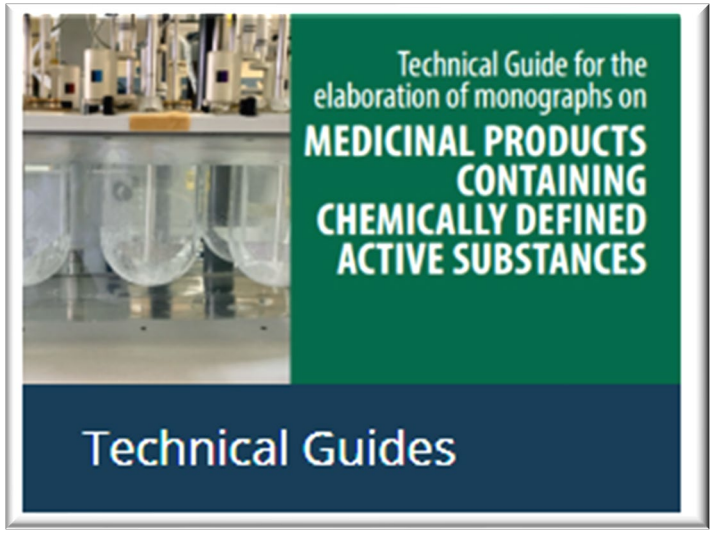
- Apply to all texts of the Ph. Eur.
- Core principles for interpretation and application of Ph. Eur. texts

General texts and chapters

- Methods of analysis & general texts
- Multi-product analytical procedures
- Given for information
- Part of the standard when referred to in a monograph

Ph. Eur. Monograph Elaboration: General Principles

- **Monograph specifications** are based on those of medicinal products currently approved by member states unless otherwise agreed by the EPC (e.g. in the case of unlicensed medicinal products)
- Approved specification(s) are the main basis for monograph elaboration, backed up by batch data
- **Analytical procedures** included in monographs are validated according to current guidelines
- All individual monographs are verified experimentally
- Draft monographs are **reviewed by stakeholders/users** including regulatory authorities, at Pharmeuropa stage
- Policy for monograph development is given in **technical guides** (available on the EDQM website)



Important concepts for analytical procedures

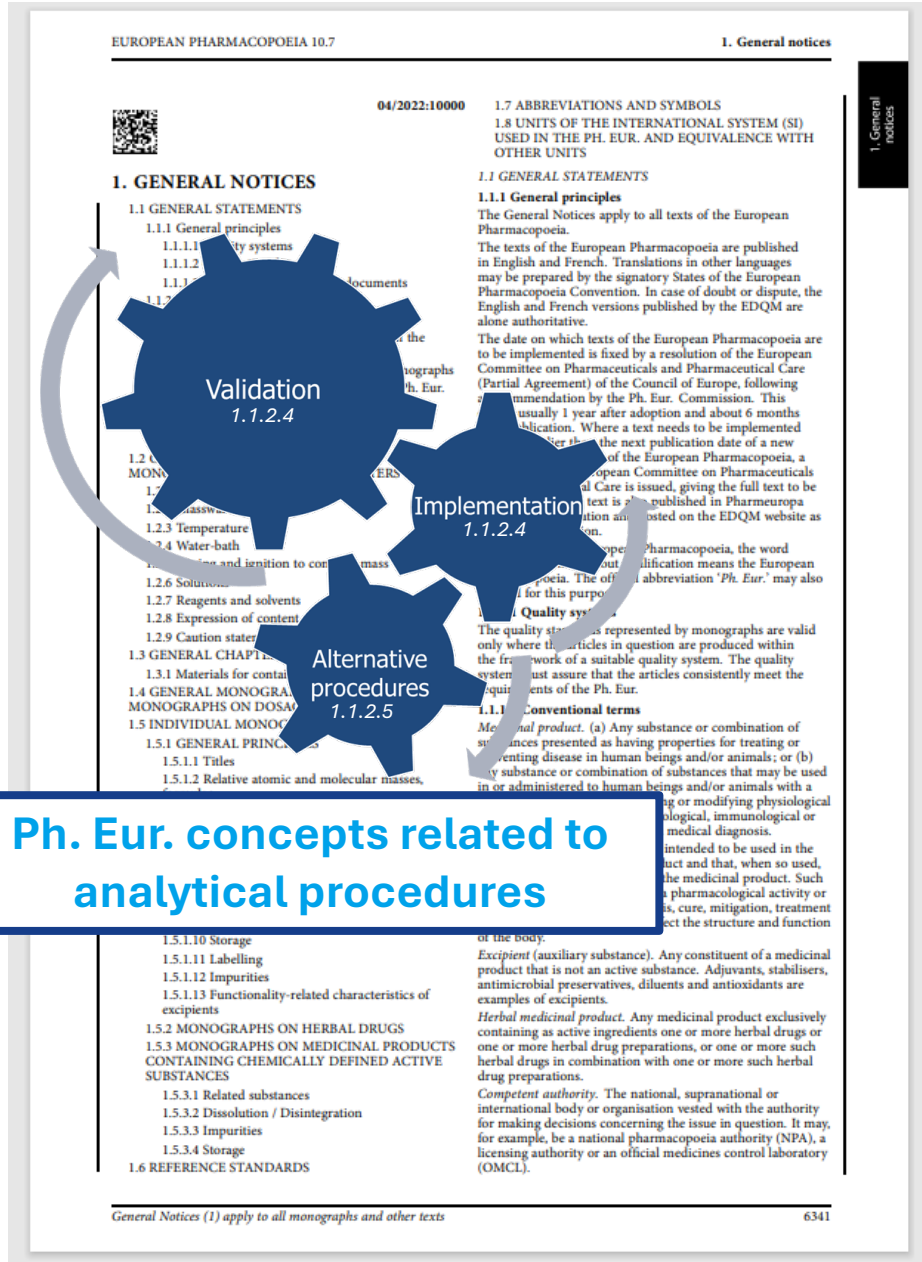
Use of alternative procedures

General Notices

At the very beginning of the Ph. Eur.

- apply to all texts including general chapters and texts
- aim at providing basic information to the user
- address **general topics**
- describes **general principles**, including *flexibility*
- include rules to understand texts, conventional expressions

Essential reading before starting to use monographs and other texts



Ph. Eur. Concepts Related to Analytical Procedures

- **Ph. Eur. Chapter 1 *General Notices*:**

1.1.2.4 Validation and implementation of Ph. Eur. analytical procedures

The analytical procedures given in an individual monograph have been **validated** in accordance with accepted scientific practice and recommendations on analytical validation. Unless otherwise stated in the individual monograph or in the corresponding general chapter, validation of these procedures by the user is not required.

When **implementing** a Ph. Eur. analytical procedure, the user must assess whether and to what extent its suitability under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.

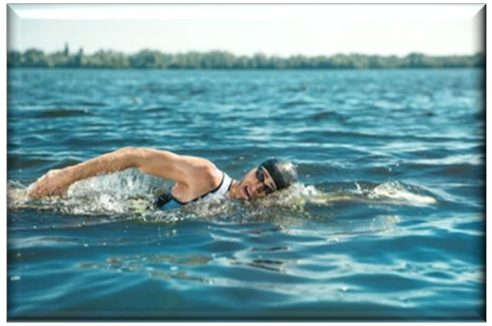
1.1.2.5 Alternative analytical procedures

*The tests and assays described are the official analytical procedures upon which the **standards** of the Ph. Eur. are based. With the **agreement of the competent authority**, alternative analytical procedures may be used for control purposes, provided that they enable an **unequivocal decision** to be made as to whether compliance with the standards of the monographs would be achieved if the official procedures were used. In the event of **doubt or dispute**, the analytical procedures of the Ph. Eur. are **alone authoritative**.*

Concept of „Alternative”

The TASK: cross the river

Ways of reaching the other side



Basic

Improved

Advanced

Pharmacopoeial procedure: legally binding, robust, established, widely accessible

Alternative analytical procedure:

- Different approach
- Comparability needs to be demonstrated

Alternative

Key Aspects of General Chapter 5.27

Framework

- Published for information
- Guidance on possible approaches
- No new requirements introduced
- ‘Comparability’ ≠ ‘equality’

5.27. COMPARABILITY OF ALTERNATIVE ANALYTICAL PROCEDURES

This general chapter is published for information. It
an alternative analytical procedure to a pharmacop
demonstrated. Other approaches to demonstrating c
The use of an alternative procedure is subject to autho
The final responsibility for the demonstration of compara
the successful outcome of the process needs to be demonstrated and documented to the satisfaction of the competent authority. Comparability must be maintained over the lifecycle of both the pharmacopoeial and alternative

Scope

- Cases where a pharmacopoeial (official) analytical procedure, as referenced in an individual monograph, would be replaced by an alternative (“in-house”) analytical procedure
- Applies to qualitative and quantitative analytical procedures

Not in scope

- Development of new analytical procedures
- Application of pharmacopoeial analytical procedures to articles not covered by Ph. Eur.

General Chapter 5.27: Preamble

*This general chapter is **published for information**. It describes how the comparability of an alternative analytical procedure to a pharmacopoeial analytical procedure may be demonstrated. Other approaches to demonstrating comparability may also be appropriate. The use of an **alternative procedure is subject to authorisation by the competent authority**. The **final responsibility** for the demonstration of comparability **lies with the user** and the successful outcome of the process needs to be demonstrated and documented to the satisfaction of the competent authority. Comparability must be **maintained over the lifecycle** of both the pharmacopoeial and alternative analytical procedure.*

General Chapter 5.27: Introduction

- **Tests and assays described in monographs are the official analytical procedures** upon which the standards of the Ph. Eur. are based.
- **With the agreement of the competent authority**, alternative analytical procedures may be used for control purposes, provided that they enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official analytical procedures were used.
- The chapter aims to provide guidance on possible approaches to the assessment of the comparability of an alternative procedure that is used instead of a pharmacopoeial procedure.
- **In the event of doubt or dispute, the analytical procedures of the Ph. Eur. are alone authoritative.**
- Comparability of alternative microbiological methods is covered in general chapter ***5.1.6. Alternative methods for control of microbiological quality***.
- Specific guidance to facilitate the use of *in vitro* methods as substitutes for existing *in vivo* methods for testing vaccines is given in general chapter ***5.2.14. Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccines***

Preliminary Conditions: Comparability Assessment

Alternative analytical procedure (validated)

Pharmacopoeial procedure (implemented)

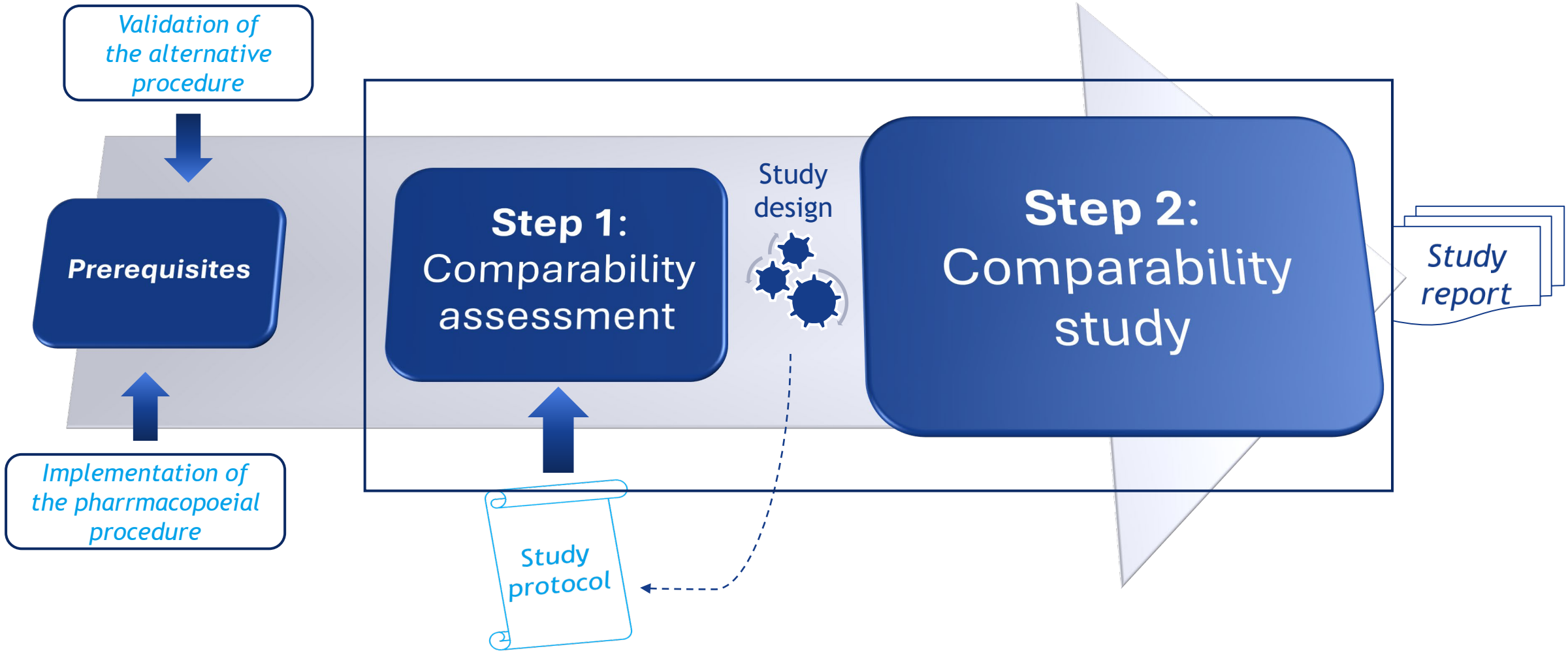
Comparison of analytical procedure performance

Demonstration the alternative procedure meets its performance criteria during **validation** is not sufficient to imply comparability with pharmacopoeial procedure.

Comparability assessment of data generated during implementation of pharmacopoeial procedure and validation studies on alternative procedure:

- APPCs, such as **specificity/selectivity, sensitivity** (at the lower range limit), **linearity** and **range** should be assessed to ensure that the alternative procedure is at least as capable as the pharmacopoeial procedure
- Outcome of the comparability assessment may form the basis for the design of the *comparability study*

Process



Comparability process

Step 1: Comparability assessment

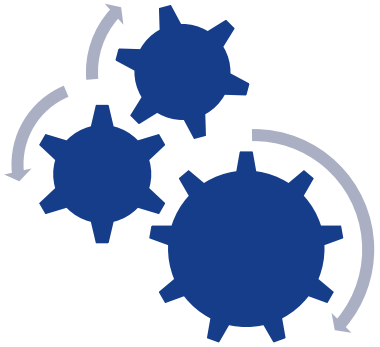
- Comparison of data obtained in the implementation of the pharmacopoeial procedure and validation data in terms of analytical procedure performance characteristics (APPCs)

Step 2: Comparability study

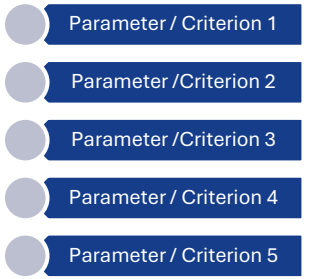
- Head-to-head testing, with the aim of reaching the same analytical decision
  → particularities: same experiments, same samples

Study design

- Based on the outcome of the comparability assessment
- Considers special cases where testing in a head-to-head format is not feasible

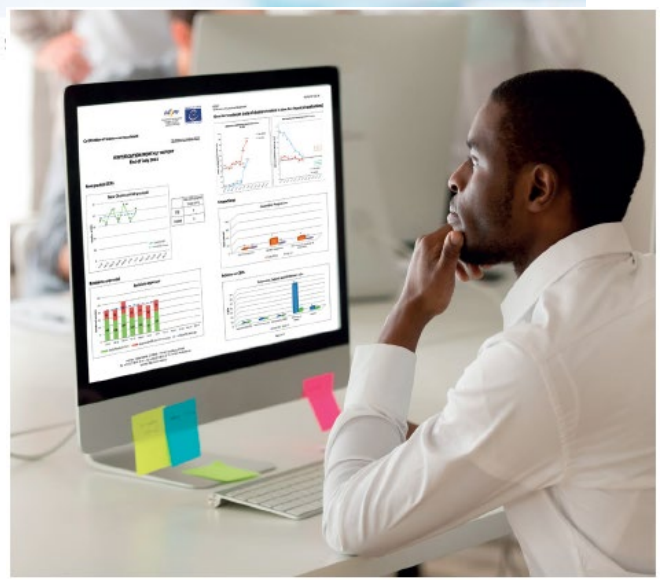


- **Study protocol**
  - Is established on the basis of the study design
  - Covers selection of samples and sample size, APPCs to be included and method for statistical evaluation of data
  - Includes definition of comparability through setting of **equivalence margin(s)** and **acceptance criteria** and their justification



- **Study report:**
  - summarises the results and conclusion of the comparability study, as well as other relevant information (e.g. deviations from study protocol, newly obtained information on the procedure(s) and or tested samples)

Acceptance criteria for comparability

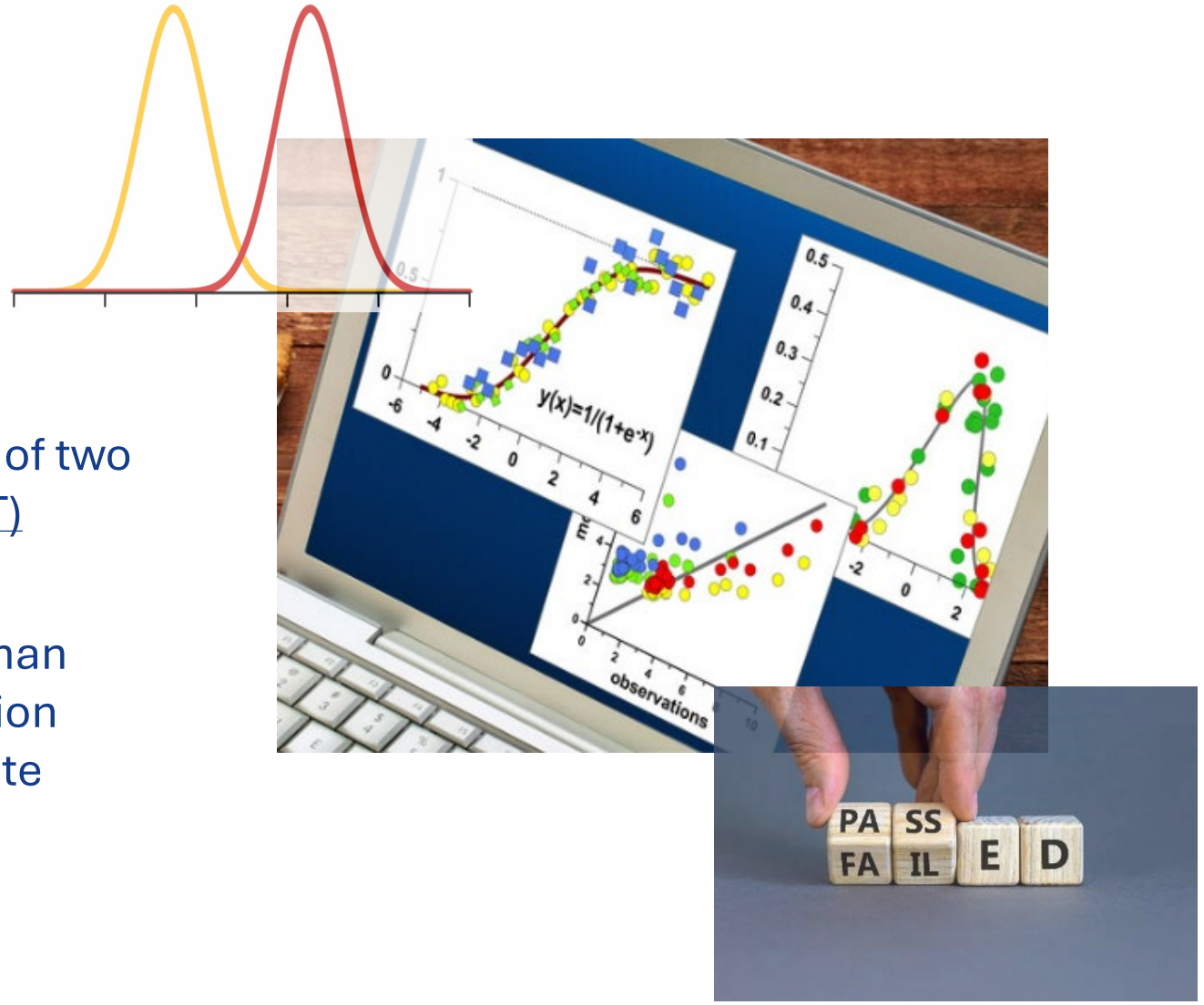


- Defined in the study design phase and stated in the study protocol
- **Equivalence margin:** the acceptable difference between the means of results from two procedures, which includes an acceptable confidence level
- Determined by a combination of scientific knowledge and statistical expertise

Statistical evaluation of results

Statistical evaluation of results

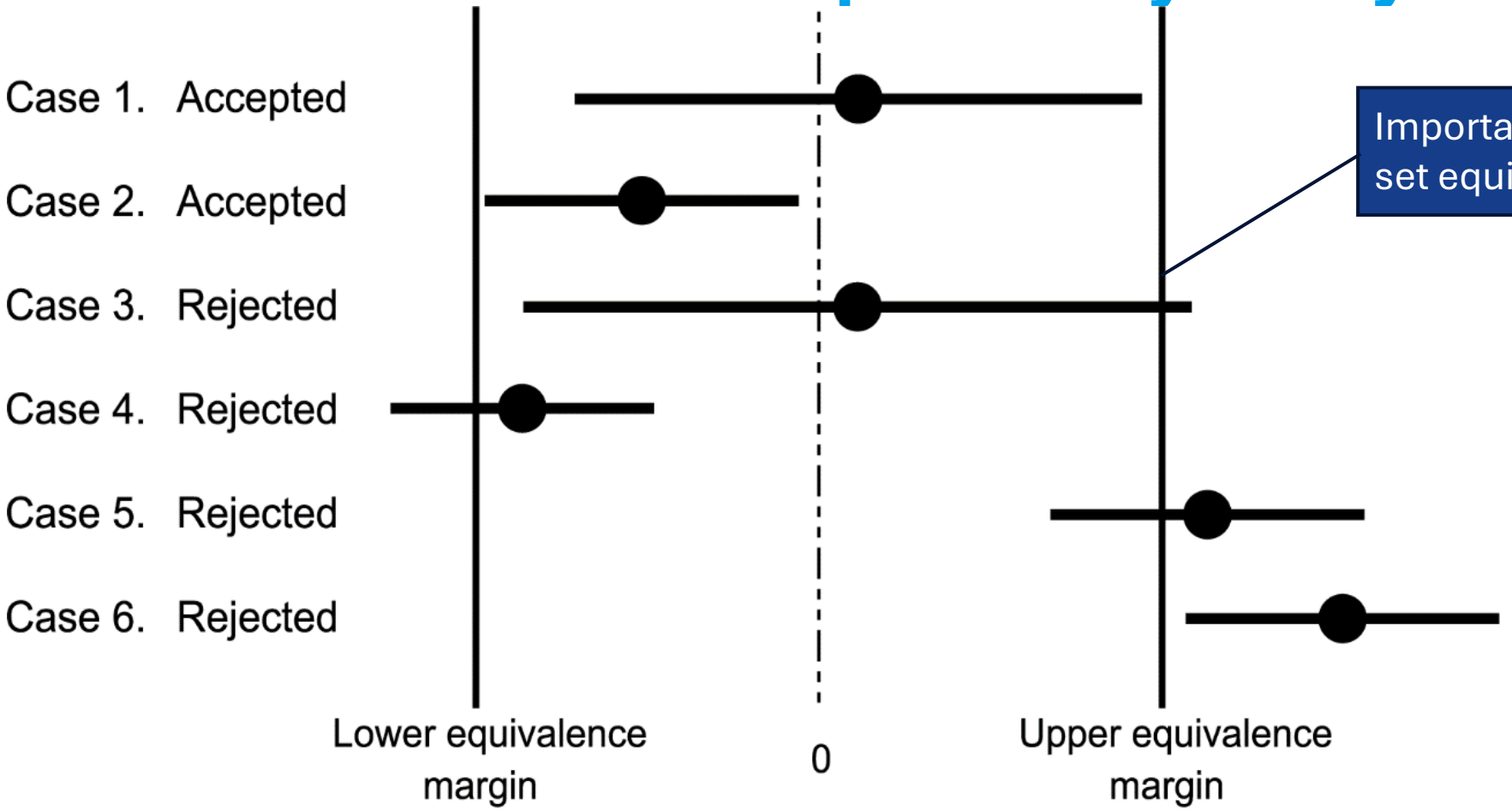
- *Step 1. Data description*
- *Step 2. Statistical assumptions*
- *Step 3. Equivalence testing*



- For quantitative results: example (most commonly used approach) - Comparison of two group means: <u>two one-sided t-tests (TOST) method</u>
- For results spreading over a wider range than those obtained at a single level, a regression approach (e.g. Deming regression, bivariate least squares regression)

- Other approaches may be appropriate
- **Pass/Fail criterion is key**

Typical outcomes of a comparability study



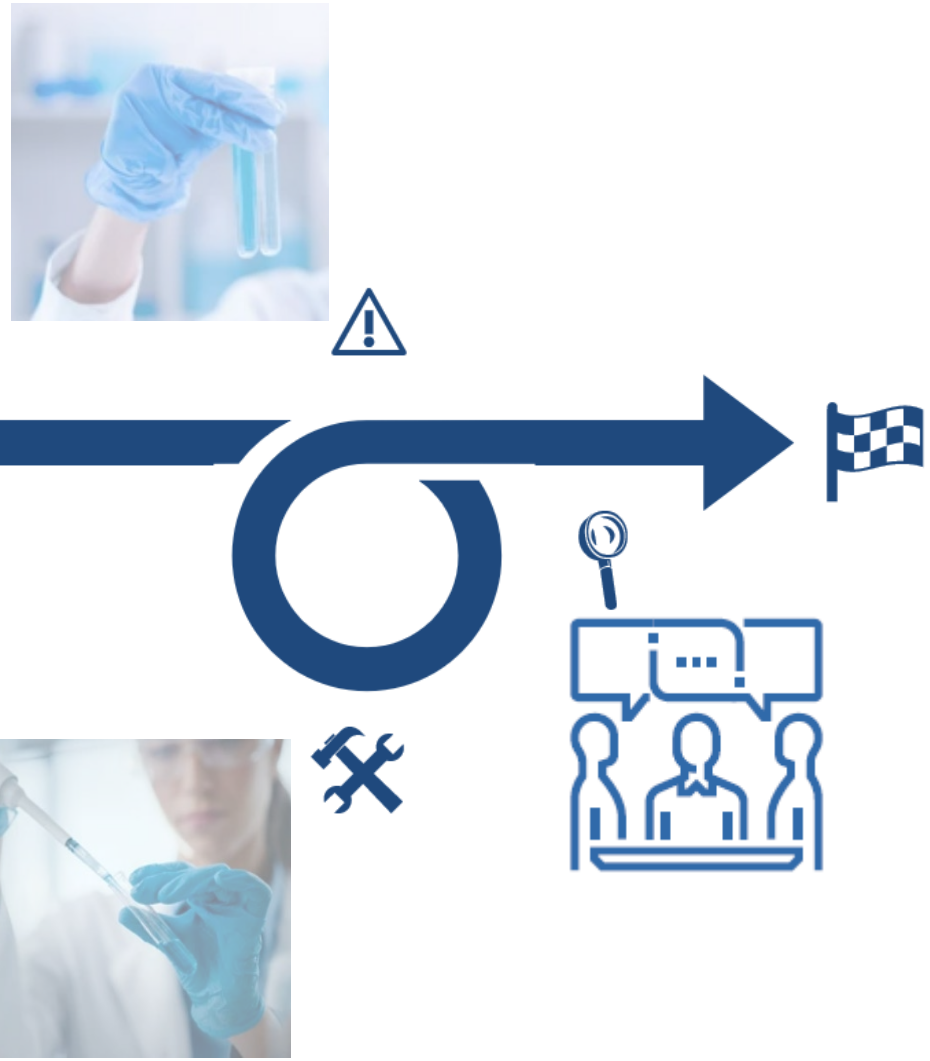
Importance of correctly set equivalence margin!

- When the equivalence as part of the comparability study is accepted, the alternative procedure may be considered statistically equivalent to the pharmacopoeial procedure.

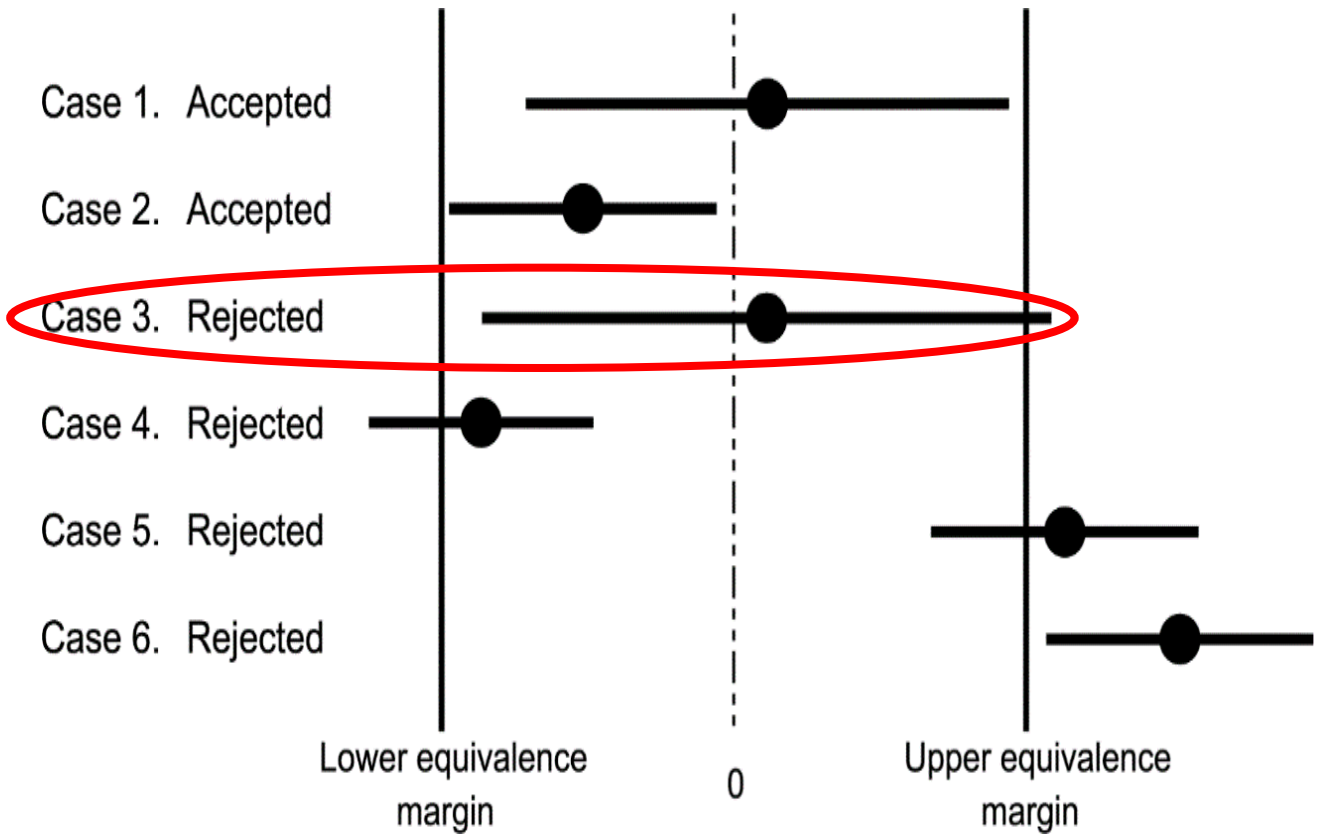
Unexpected outcome

In cases where the comparability cannot be accepted directly, certain flexibility is present:
- available data may be reviewed and if bias and/or variability is observed and steps taken to reduce it, the assessment may be relaunched, including e.g. performing additional experiments.

This possibility needs to be clearly defined in the study protocol.



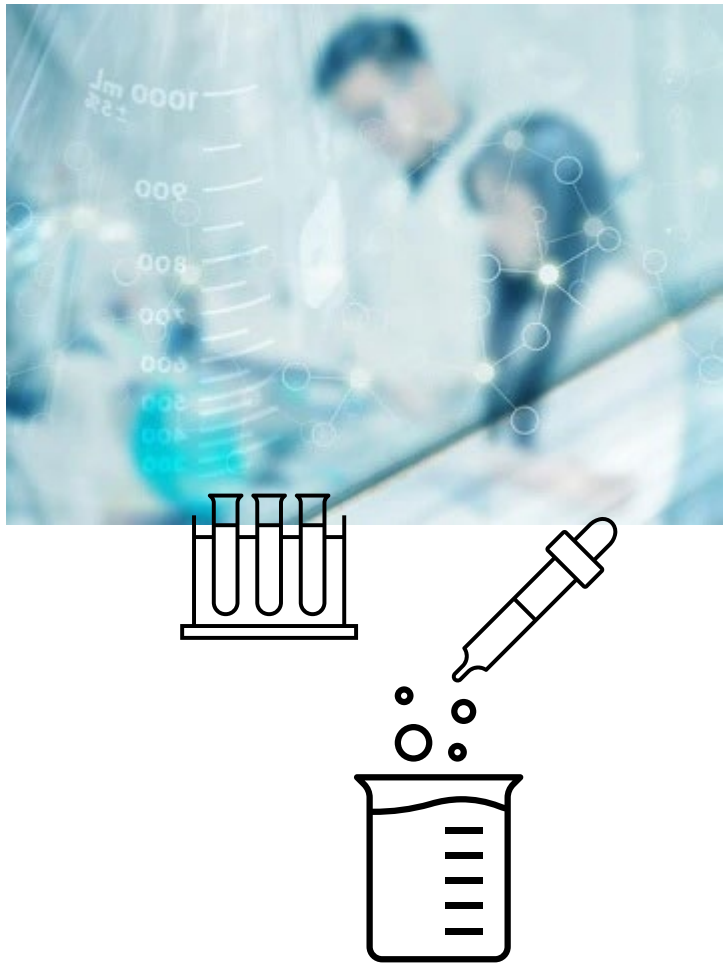
Unexpected outcome (continued)



Case 3: Potential for acceptance

- Identify the root cause for the high variability of the results
- Can its influence be reduced or negated?
- Perform additional experiments after addressing the root cause
- E.g. better precision with more replicates → the outcome changes to accepted.

Practical aspects – Representative samples



- How to choose representative samples:

  - head-to-head testing of same homogeneous, authentic (i.e. non-spiked) samples preferred

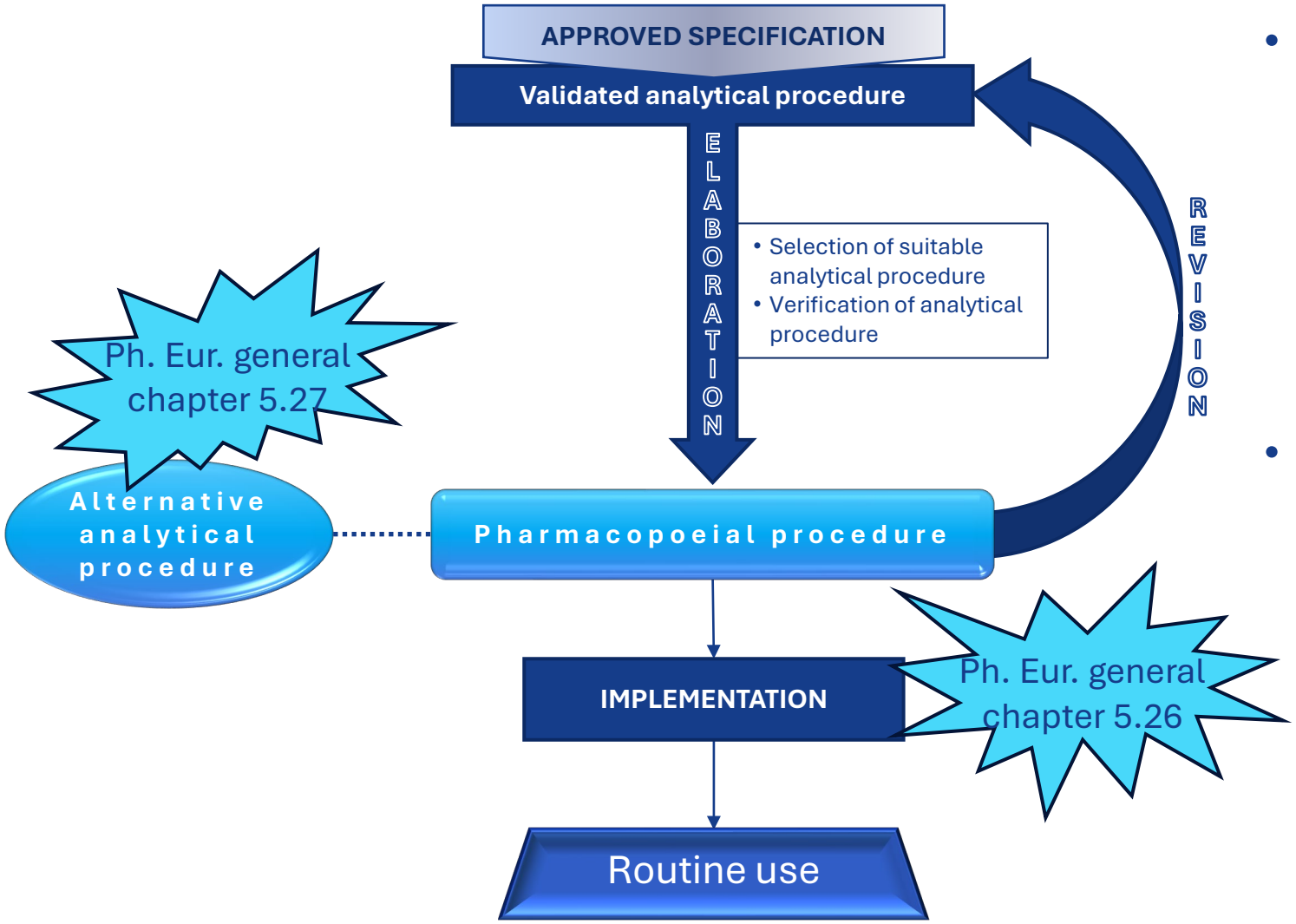
  - synthesised (spiked) samples or forced degradation are an option

  - variability of samples and sample matrices needs to be considered

  - it may be useful to include samples at or near the specification limit and/or reporting threshold

- Depending on the intended purpose of the procedures, useful comparability information for certain APPCs may be generated in the comparability study by analysing Ph. Eur. reference standards using the alternative procedure.

Lifecycle of the Pharmacopoeial Procedure



- If a user considers the alternative analytical procedure to bring significant improvement for the quality of the article, they are encouraged to contact EDQM and/or submit a **request for a revision** via the NPA
- In the event of an issue with a pharmacopoeial procedure (e.g. implementation difficulties), EDQM should be contacted via the Helpdesk and if confirmed, this may result in a revision
  → **In itself not a case for an alternative procedure**

Task completed!

- Or is it? Reminder:

Agreement of the competent authority needed!

- Comparability needs to be maintained over the lifecycle of both procedures

Join us!

- Pharmaceutical scientists
- Analytical chemists
- Biologists
- Quality assessors
- Inspectors
- Quality assurance professionals
- And much more!